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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 03/26/04 RK

Office Action Summary	Application No.	Applicant(s)	
	10/058,291	HARTLEY ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 35-100 are pending and under consideration in this Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 52-68 and 87-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

The broadest claim is drawn to a nucleic acid comprising a functional antibiotic resistance gene, where *any* recombination site separates a first and second portion of the antibiotic resistance gene. The recombination site can reasonably be interpreted to comprise *any* site from *any* source and be of *any* type. Notwithstanding the separation of the two portions by a recombination site, the nucleic acid comprises a functional antibiotic resistance gene. Even in the most specific embodiments, the first portion of the antibiotic resistance gene is a promoter sequence and the recombination site is a lox or att site or mutants thereof. Therefore a recombination sequence comprising some sequence from lox or att (e.g. mutant) would satisfy the claim limitation.

Additionally, the lox site can be a loxP site. A reasonable interpretation of the term "loxP" is that it can be read broadly to encompass any functional variant of loxP that can be specifically recombined by the Cre recombinase (e.g. having the requisite Cre binding site). Therefore, the rejected claims encompass an enormous genus of nucleic acids that comprise a functional antibiotic resistance gene, notwithstanding the intervening recombination site sequences. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The teachings of the specification appear to be limited to site-specific recombination sites utilized in a technique for recombinational cloning wherein the first portion of antibiotic resistance gene (e.g. Kanamycin; "Km") comprises a regulatory sequence (e.g. repressor-specific binding site) and the second portion is the Km gene, each separated from the other by a site-specific recombination site, so that when the repressor binding site and repressor are present, then cells containing the Km gene remain sensitive to the antibiotic. (Spec. p. 44, Example 5). The specification does not provide a basis for the skilled artisan to envision other embodiments of the claimed invention wherein the nucleic acid encoding a functional antibiotic resistance gene, comprises a first portion and second portion separated by *any* recombination site sequence. For example, most of the rejected claims encompass embodiments where the nucleic acid simultaneously comprises a site-specific recombination site (e.g. LoxP) inserted into a protein

coding sequence such that the nucleic acid encodes a functional protein and is capable of site-specific recombination.

Given the enormous breadth of the nucleic acids encompassed by the rejected claims, and given the limited description from the instant specification of such nucleic acids, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of nucleic acids. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 39-68 and 79-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39, 43-45, 52, 55-56, 58-60 and 67-68 recite the limitation "recombination site". The term does not appear to be explicitly defined in the instant specification. This term is vague and indefinite in that it is unclear if the term is meant to encompass literally any nucleic acid that might serve as a site for a recombination (e.g. homologous, non-homologous recombination, etc.) or is meant, as appears to be the case upon reading the specification, a site-specific recombination sequence? Dependant claims drawn to nucleic acids *comprising* site-specific

sequences (e.g. loxP) remain vague and indefinite, because such nucleic acids may contain sequences at the recombination site in addition to the site-specific sequence.

Claim 40 recites, "said first recombination site". There is insufficient antecedent basis for the term "first" in the claim. The base claim recites "at least one recombination site", conferring further ambiguity as to which recombination site would be the "first" one.

Claim 47 and 62 recite the limitation "one cloning site". The term does not appear to be explicitly defined in the instant specification. The term is vague and indefinite in that it is unclear what the term encompasses. Does applicant intend that the term be drawn to recombination sites or restriction enzyme sites?

Claims 67 and 68 recite the limitation "adjacent". The term does not appear to be explicitly defined in the instant specification. The term is vague and indefinite in that it is unclear what the term encompasses. Does applicant intend the term be drawn to mean immediately adjacent (i.e. no intervening bases)?

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 35-50, 69-70, 72-73, 75-87 and 98-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Dale and Ow (PNAS, 1991, 88:10558-62; whole document; hereinafter "Dale").

The broadest claim (35) is drawn to a nucleic acid molecule comprising a *lox* site flanked by one promoter and one antibiotic resistance gene. More specific claims are drawn to a nucleic acid molecule comprising a recombination site separating a first and second portion of a

functional antibiotic resistance gene. In addition, more specific claims are drawn to a nucleic acid comprising a lox site flanked by a promoter and an antibiotic resistance gene, where the promoter and resistance gene are operably linked. The lox site can be a loxP site. Furthermore, a recombination site can separate a promoter and antibiotic resistance gene in the claimed nucleic acid. The nucleic acid can comprise an additional recombination site that can be a *lox* or *att* site, more particularly being a *loxP* site.

In addition, the nucleic acid molecule can be a vector or an expression vector. The claims are also drawn to host cells comprising the claimed nucleic acid compositions.

Dale teaches nucleic acid composition comprising an antibiotic resistance gene flanked by recombination sites, further containing a promoter sequence and transformed into a host organism. (e.g. p. 10558, col. 2, ¶ 1). More specifically, Dale teaches that the nucleic acid comprises a loxP site separating a promoter (35s) and an ampicillin resistance gene, where the promoter and resistance gene are operatively linked. (e.g. p. 10559, Fig. 1). In addition, the nucleic acid comprises a second recombination site – loxP. (e.g. p. 10559, Fig. 1). The nucleic acid molecule is a plasmid vector (pED53) that is used to transform *E. coli* host cells. (e.g. p. 10558, bridging ¶ to p. 10559). In addition, Dale teaches nucleic acid molecules comprising an expression vector (expressing chimeric *luc* gene). (e.g. p. 10559, Fig. 1). In sum, Dale anticipates the rejected claims.

4. Claim 35-50, 52-65, 67-70, 72-73 and 75-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Palazzolo et al. (Gene, 1990; 88:25-36; whole document; hereinafter Palazzolo).

The broadest claim (35) is drawn to a nucleic acid molecule comprising a *lox* site flanked by one promoter and one antibiotic resistance gene. More specific claims are drawn to a nucleic acid molecule comprising a first and second portion of a functional antibiotic resistance gene separated by a recombination site, where the first and second portion are operably linked and where the first portion is a promoter. More particularly the nucleic acid molecule has at least one additional recombination site, at least one cloning site, and the recombination sites can be loxP sites. Furthermore, the first and second portion are adjacent to the recombination site. In addition, the nucleic acid molecule is a vector, more particularly an expression vector.

Palazzolo teaches a nucleic acid molecule constructed for recombinational sublconing using the Cre-loxP system. (e.g. Abstract). More specifically, Palazzolo teaches an expression vector nucleic acid molecule comprising a first portion (SP6 promoter) separated by a loxP site and operatively linked to an antibiotic resistance gene (i.e. bla or Ampicillin resistance). (e.g. p. 30, Fig. 4, Legend and depiction of λ EXLX construct). In addition, the construct has a second recombination site – loxP. (e.g. p. 30, Fig. 4, last schematic; depicting SP6 promoter flanked by two loxP sites). Furthermore, the cloning vectors are used to transform *E. coli* hosts. (e.g. Abstract; p. 26, col. 2, ¶ 2; p. 27, col. 2, last ¶). Moreover, interpreted as broadly as reasonable, the first and second portion (i.e. SP6 promoter and *bla* gene) are adjacent to the recombination sites. In sum, Palazzolo anticipates the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 51, 66, 71 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Palazzolo et al. (Gene, 1990; 88:25-36; whole document; hereinafter Palazzolo) further in view of Lenski et al. (J. Bacter. 1994 June; 176(11):3140-3147; whole document; hereinafter Lenski).

The claims are drawn to nucleic acid molecules where a recombination site separates a first portion and a second portion of an antibiotic resistance gene, which is limited to chloramphenicol.

Palazzolo teaches all the limitations, as discussed above, but it does not teach the antibiotic resistance gene being chloramphenicol.

Lenski teaches that chloramphenicol resistance is one of many antibiotic resistance genes that can be used in subcloning involving *E. coli* hosts. (e.g. p. 3140, col. 1, bridging ¶ to col. 2; p.

3141, Table 2). Therefore, Lenski teaches, that amongst other antibiotic resistance genes, chloramphenicol is an effective selection marker.

It would have been obvious to modify the nucleic acid constructs that Palazzolo teaches with a relatively routine substitution with a different selection marker (i.e. chloramphenicol). One of ordinary skill in the art, at the time of applicant's invention would have been motivated to use various antibiotic resistance genes, including chloramphenicol, known as effective selection markers, to expand the range of selection markers that could be used with various strains of *E. coli*. Therefore, the skilled artisan, in seeking to expand the range of selection markers, would have been motivated to modify the nucleic acid molecules taught by Palazzolo to also encode chloramphenicol resistance, as taught by Lenski, as one of many potential selection markers effective in bacterial hosts such as *E. coli*. Given the level of the skill of the ordinary skilled artisan and the teachings of the cited art, at the time of applicant's invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in making a nucleic acid molecule comprising first and second portions of a chloramphenicol antibiotic resistance gene.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER